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(54) Process for the preparation of purine derivatives

Verfahren zur Herstellung von Purinderivaten

Procédé pour la préparation de dérivés de purine

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(56) References cited:
EP-A- 0 141 927
EP-A- 0 182 024
EP-A- 0 302 644
WO-A-87/05604

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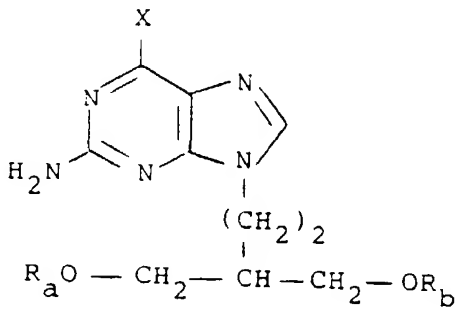
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 352 953 B1

Description

[0001] The present invention relates to a novel process for the preparation of purine derivatives which have antiviral activity.

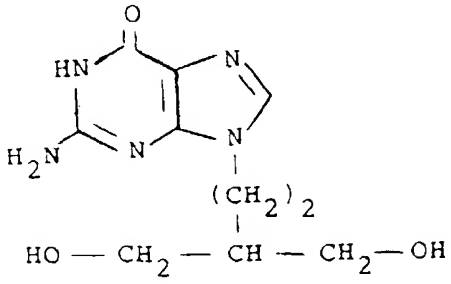
[0002] EP-A-141927 and EP-A-182024 (Beecham Group p.l.c.) describe, inter alia, compounds of formula (I) and pharmaceutically acceptable salts thereof:



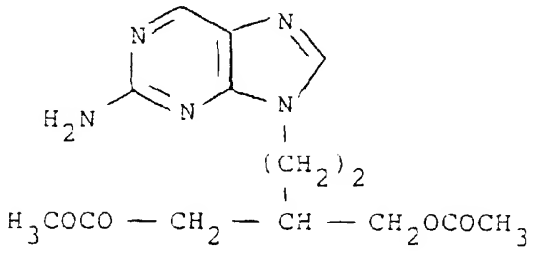
(I)

wherein X is hydrogen or hydroxy and R_a and R_b are independently hydrogen or a group RCO- wherein R is phenyl or C_{1-18} alkyl.

[0003] The compounds of formulae (A) and (B); wherein X is OH and R_a and R_b are both hydrogen (BRL 39123); and wherein X is hydrogen and R_a and R_b are both acetyl (BRL 42810), are of particular interest as potential antiviral agents.

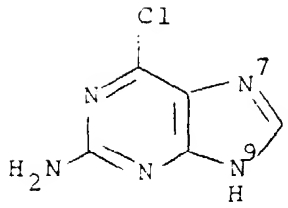


(A)



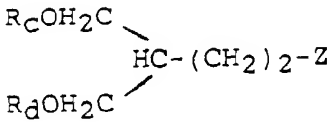
(B)

[0004] The process already described for the preparation of the above compounds involves the reaction of 2-amino-6-chloropurine of formula (C):



(C)

with a side chain intermediate of formula (D):



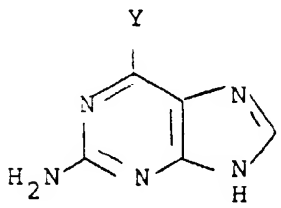
(D)

wherein R_c and R_d are independently acyl groups or hydroxy protecting groups and Z is a leaving group, such as halo, for example chloro, bromo, iodo; and thereafter converting the 6-chloro group to hydroxy by means of hydrolysis, or to hydrogen by means of reduction.

[0005] The disadvantage with this process is that the use of the intermediate of formula (C) results in a mixture of products i.e. that when the side chain is attached at N-9 and the undesired product wherein the side chain is attached at N-7. This can result in low yields of the desired N-9 product.

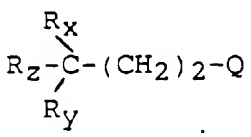
[0006] It has surprisingly been discovered that, if the 6-chloro group in the compound of formula (C) is replaced by an iodo group, a diphenylmethylthio or a benzylthio group wherein the phenyl moiety is optionally substituted by one or two groups selected from C_{1-4} alkyl, halo and C_{1-4} alkoxy, the ratio of N-9 product to N-7 product is increased, providing a better overall yield of the resulting compound of formula (I).

[0007] Accordingly, the present invention provides a process for the preparation of a compound of formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



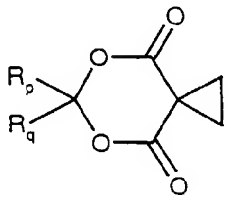
(II)

wherein the amino group is optionally protected, Y is iodo, diphenylmethylthio or benzylthio wherein the phenyl moiety is optionally substituted by one or two groups selected from C_{1-4} alkyl, halo and C_{1-4} alkoxy, with a compound of formula (III):



(III)

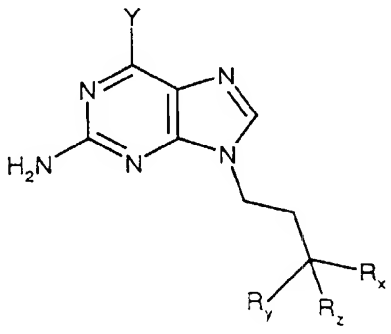
wherein Q is a leaving group, R_x and R_y are protected hydroxymethyl or acyloxymethyl, or group(s) convertible to hydroxymethyl or acyloxymethyl; and R_z is hydrogen or a group convertible thereto; or a compound of formula (IIIA):-



(IIIA)

wherein R_p and R_q are independently hydrogen, C_{1-6}alkyl or phenyl, or R_p and R_q together are C_{4-6} polymethylene; and thereafter converting Y to X is hydroxy by means of hydrolysis, or to X is hydrogen by means of reduction; converting R_x and R_y, when other than hydroxymethyl or acyloxymethyl, to hydroxymethyl or acyloxymethyl, optionally converting R_x/R_y hydroxymethyl to acyloxymethyl or vice versa, deprotecting the 2-amino group where necessary and converting R_z, when other than hydrogen, to hydrogen; and optionally forming a pharmaceutically acceptable salt thereof.

[0008] The intermediates formed in this reaction are of formula (IV):



(IV)

which are novel and form an aspect of the invention.

[0009] The reaction may be carried out in an inert solvent, for example dimethylformamide, dimethylsulphoxide or acetonitrile, preferably dimethylformamide, in the presence of an inorganic or organic base, over a temperature range from 0°C to the boiling point of the solvent, usually 30-40°C. Examples of inorganic bases include alkali metal hydrides, alkali metal carbonates such as sodium or potassium carbonate and preferably potassium carbonate. Suitable organic bases are 1,8-diazabicyclo[5.4.0]undec-7-ene and tetramethyl guanidine.

[0010] Suitable examples of optional substituents in the phenyl group Y when benzylthio are one or two groups selected from C_{1-4} alkyl, halo and C_{1-4} alkoxy. Halo includes iodo, bromo, chloro and fluoro, and alkyl/alkoxy groups include those containing methyl, ethyl, n and iso-propyl. Y may also be diphenylmethylthio, optionally substituted in the phenyl ring(s) as defined for Y when benzylthio. Y is preferably iodo or benzylthio, most preferably iodo.

[0011] Suitable examples of the leaving group Q, include halo, such as chloro, bromo or iodo, and tosyloxy and mesyloxy.

[0012] Suitable examples of hydroxy protecting groups (other than acyl groups) include the t-butyl dimethylsilyl group removable by 80% acetic acid at elevated temperatures, around 90°C, or by treatment with tetrabutyl ammonium fluoride in a solvent, such as tetrahydrofuran, at ambient temperature.

[0013] Another suitable protecting group is wherein the two hydroxy groups in formula (III) (when R_x is hydroxymethyl) are reacted with 2,2-dimethoxypropane, forming a 1,3-dioxan ring. This group may be removed by acidic hydrolysis.

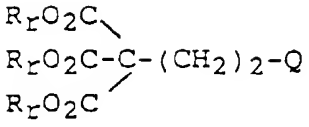
[0014] Other suitable protecting groups include substituted benzyl groups such as p-methoxybenzyl, removable by treatment with 2,3-dichloro-5,6-dicyanobenzoquinone.

[0015] Other suitable protecting groups are apparent to those skilled in the art.

[0016] R_x and/or R_y may be acyloxymethyl, such as a group RCO_2CH_2 wherein R is as defined in formula (I). Examples of R include methyl, ethyl, n- and iso-propyl, n- and iso-, sec- and tert-butyl, preferably methyl.

[0017] Interconversion of R_x/R_y acyloxymethyl and hydroxymethyl may be carried out conventionally as described in EP-A-141927.

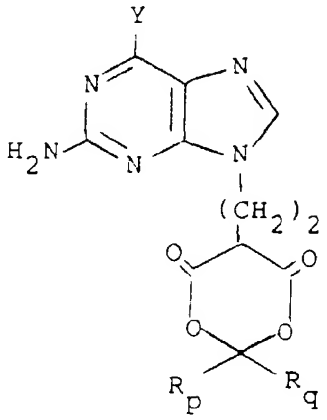
[0018] Other suitable values of R_x, R_y, R_z include wherein the compound of formula (III) is of formula (IIIB):



(IIIB)

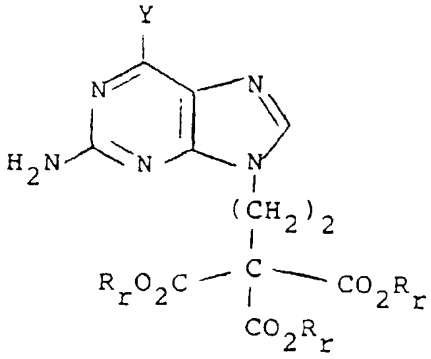
wherein R_r is C_{1-6} alkyl or phenyl C_{1-6} alkyl, in which any phenyl moieties are optionally substituted, (as defined for Y hereinbefore when thiobenzyl).

[0019] When the compound of formula (IIIA) is used, the resulting intermediate is of formula (IVA):



(IVA)

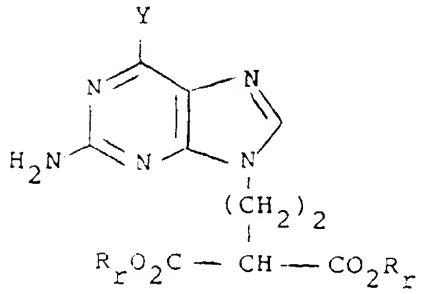
[0020] When the compound of formula (IIIB) is used, the resulting intermediate is of formula (IVB):



(IVB)

[0021] Values for R_p and R_q and R_r include these values listed as suitable for R in formula (I), preferably methyl for R_p and R_q and ethyl for R_r. In addition R_p and R_q may together be C_4 or C_5 polymethylene.

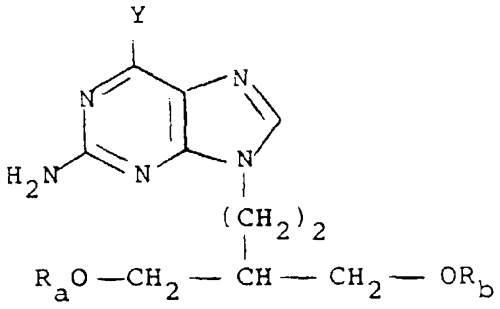
[0022] The intermediates of formulae (IVA) and (IVB) are subsequently converted to an intermediate of formula (V):



(V)

by transesterification and hydrolysis/decarboxylation respectively, as described in the Examples hereinafter.

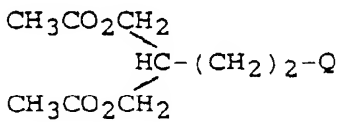
[0023] An intermediate of formula (V) is convertible to a compound of formula (VI):



(VI)

by reduction, under conventional conditions using, for example, sodium borohydride.

[0024] It is preferred, however, that the intermediate of formula (III) is of formula (III)':



(III)'

for the preparation of compounds of formula (A) and (B) as defined, because:

i) Compounds of formula (III)' give a particularly good N9:N7 ratio (regioselectivity).
ii) Ease of separation of N9:N7 isomers.
(iii) The same intermediate of formula (III)' is used for the preparation of compounds of the formula (A) and formula (B).

[0025] The 2-amino group may be protected, for example, using a benzyl protecting group, removable by hydrogenolysis. It may also be protected by an acyl group, for example acetyl, removable by hydrolysis, or a Schiff's base, e. g. benzylidene, removable by acid hydrolysis.

[0026] Pharmaceutically acceptable salts are formed conventionally.

[0027] Intermediates of formula (III) wherein R_x/R_y are protected hydroxymethyl or acyloxymethyl may be prepared as described in EP-A-141927 or by analogous methods thereto.

[0028] Intermediates of the formula (IIIA) are known or are prepared by analogous methods, such as that described in Organic Syntheses Vol 60, page 66.

[0029] Intermediates of formula (IIIB) are known or prepared by analogous methods. The compound of formula (IIIB) wherein Q is bromo and R_r is ethyl may be prepared from triethyl methanetricarboxylate according to the procedure

described by H. Rapoport et.al., J. Org. Chem., 44, 3492(1979).

[0030] Intermediates of the formula (II) wherein Y is iodo or a benzylthio group may be prepared from the compound of formula (C). When Y is iodo, the preparation is by reaction with HI in a transhalogenation reaction, preferably using a cosolvent, such as acetone. When Y is optionally substituted thiobenzyl the preparation is by reaction with HY.

[0031] The following Examples illustrate the invention.

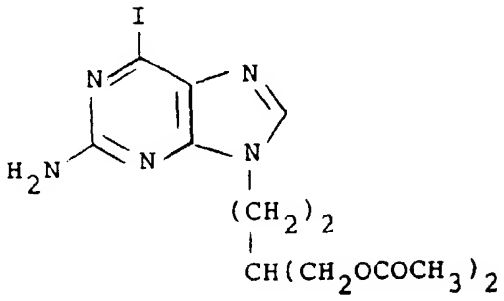
[0032] BRL 39123 and/or BRL 42810 may be prepared from the intermediates of Examples 2a), 3b), 4b), 5b), 6b), 7 and 8) according to the methods herein described.

[0033] When used therein, the Examples which incorporate the term '100 p.s.i', expressed in SI units is : 6.895×10^5 Nm^{-2}.

Example 1

a) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine

[0034]



Preparation 1

[0035] 2-Acetoxymethyl-4-iodobut-1-yl acetate (3.14g) was added to a stirred suspension of 2-amino-6-iodopurine (2.61g) and anhydrous potassium carbonate (2.08) in N,N-dimethylformamide (50cm^3) and the resulting mixture stirred at ambient temperature for 18 hours. T.l.c. (5% methanol-dichloromethane) showed two products, rf = 0.24 and 0.47; corresponding to the N7- and N9-alkylated purines.

[0036] The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (50cm^3). Evaporation of the filtrate gave a pale coloured solid. Purification via column chromatography on silica (100g) [eluant 2.5% methanol-chloroform] gave the title compound 3.55g (79.4%) and 0.4g (8.9%) of the corresponding 7-isomer. m.p. (of title compound) 116-117°C

[0037] ^{1}H n.m.r. (D_6DMSO): δ 1.90 (m, 3H,-C$\underline{H}_2$CH-), 2.0 (s, 6H, C$\underline{H}_3$-), 4.0(d,4H-OC$\underline{H}_2$-), 4.10 (t, 2H, -NC$\underline{H}_2$), 6.80 (brs, 2H -N$\underline{H}_2$), 8.15 (s, 1H, $\underline{H}$-8).

Preparation 2

[0038] Using the above procedure 2-amino-6-iodopurine (3.8g) and 2-acetoxymethyl-4-bromobut-1-yl acetate (4.4g) gave the title compound 5.3g (81%, m.p. 116-117°C, and 0.5g (7.7%) of the corresponding N-7-alkylated purine.

[0039] ^{1}H n.m.r., t.l.c. and m.p. consistent with the title compound.

Preparation 3

[0040] A mixture 2-amino-6-iodopurine (1.5g), 2-acetoxymethyl-4-chlorobut-1-yl acetate (1.41g) and anhydrous potassium carbonate (1.19g) in N,N-dimethylformamide (40cm^3) was stirred at 80°C overnight. When cool the pale yellow mixture was filtered and the filtrate evaporated under reduced pressure. Purification via column chromatography on silica (150g) [eluant 2% methanol-dichloromethane increasing to 4% methanol-dichloromethane] gave the title compound 2.08g (81%) and 0.136g (5.3%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine.

[0041] ^{1}H n.m.r., t.l.c. and m.p. consistent with the title compound.

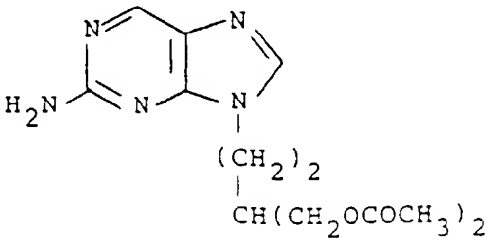
Preparation 4

[0042] Potassium bromide (6.3g) was added to a solution of 2-acetoxymethyl-4-methanesulphonyloxybut-1-yl acetate (10g) in N,N-dimethylformamide (87cm^3) and the mixture stirred at 60-70° for 2 hours. The reaction mixture was cooled to ambient temperature and 2-amino-6-iodopurine (9.1g) and anhydrous potassium carbonate (7.3g) added. The resulting suspension was stirred at ambient temperature for 48 hours. T.l.c. (5% methanol-dichloromethane) showed two products. rf=0.24, and 0.47; corresponding to the N7- and N9-alkylated purines.

[0043] Filtration and evaporation of the filtrate gave a pale coloured residue that was partioned between water (500cm^3) and dichloromethane (500cm^3). The layers were separated and the aqueous phase re-extracted with dichloromethane (2x250cm^3). The combined organic extract was dried over magnesium sulphate and evaporated to give the crude product. Purification via silica gel chromatography (eluant 2% methanol-dichloromethane increasing to 3% methanol-dichloromethane) gave the title compound 12.2g (77%), m.p. 116-117°C and 0.8g (5%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine.

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, (BRL42810)

[0044]

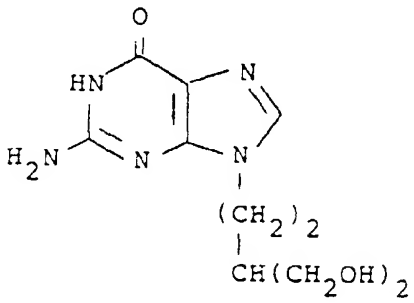


[0045] A solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine (15.3g) and triethylamine (3.8cm^3) in ethanol (200cm^3) was hydrogenated over 5% palladium on charcoal (1.6g, Englehard type 4573) at 50° and 50 psi for 4 hours. The reaction mixture was filtered and residue washed with ethanol (200cm^3). After evaporation of the filtrate to ca 50cm^3, water (150cm^3) and dichloromethane (75cm^3) was added. The phases were separated and the aqueous layer extracted with dichloromethane (3x75cm^3). The combined organic extract was dried over magnesium sulphate and evaporated to give the crude product. Recrystallisation from boiling butan-1-ol (30cm^3) gave the title compound 9.8g (89%) m.p. 102°C

[0046] ^{1}H n.m.r. ($CDCl_3$) and t.l.c. (60:40 ethylacetate: methanol) were consistent with the title compound.

c) 9-(4-Hydroxy-3-hydroxymethylbut-1-yl)guanine, (BRL39123)

[0047]



[0048] A mixture of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine (12g) and 2M-hydrochloric acid (266cm^3) was stirred under reflux for 3 hours. After cooling, a solution of sodium hydroxide (36g) in water (72cm^3) was added and the stirring continued at ambient temperature for 2 hours. The solution was neutralised with concentrated hydrochloric acid to precipitate the product. Recrystallisation from boiling water gave the title compound 6.0g (88%),

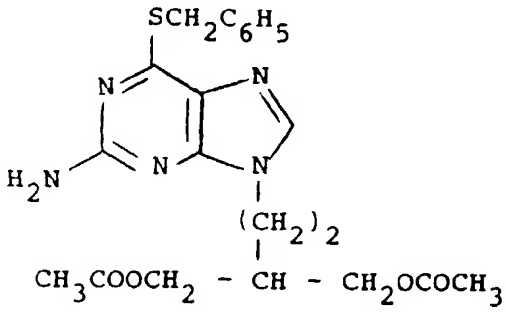
m.p. 278-280°C (dec.).

[0049] ^{1}H n.m.r. (D_6DMSO): δ 1.50 (m, 1H,-CH<), 1.75 (q, 2H CH_2-CH), 3.45 (m, 4H, -CH_2OH), 4.05 (t, 2H, -NCH_2-), 4.50 (t, 2H, -CH_2OH), 6.50 (brs, 2H, -NH_2), 7.75 (s, 1H, H-8), 10.75 (brs, 1H, -NHCO).

Example 2

a) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine

[0050]



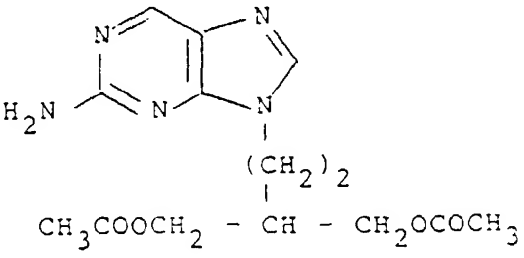
[0051] A mixture of 2-amino-6[(phenylmethyl)thio]purine[1](20g), 2-acetoxymethyl-4-iodobut-1-yl acetate (24.5g) and potassium carbonate (16.3g) in N,N-dimethylformamide (250 cm^3) was stirred at ambient temperature for 66 hours. T. l.c. (5% methanol-dichloromethane) showed two spots, rf 0.44, 0.74. The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (100 cm^3). Evaporation of the filtrate gave a pale yellow viscous gum.

[0052] Purification via silica gel chromatography (eluant 5% methanol-dichloromethane) gave the title compound 30g (87%), rf (5% methanol-dichloromethane) = 0.74, as a viscous gum. A small amount of the corresponding N7-isomer 2.4g (7%) was also isolated, rf (5% methanol-dichloromethane) = 0.44.

^{1}H n.m.r. ($CDCl_3$): δ 1.85(m, 3H,-CH_2-CH-),
2.05(s,6H,CH_3), 4.10(m,6H,NCH_2 + OCH_2-),
4.55(s,2H,$CH_2C_6H_5$), 5.15(brs,2H,NH_2),
7.25(m,3H,C_6H_5), 7.40(d,2H,C_6H_5), 7.65(s,1H,H-8).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-aminopurine, (BRL 42810)

[0053]



[0054] Raney nickel (4g) was added to a solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine (10g) in ethanol (250 cm^3) and the mixture treated with hydrogen (100 psi) at 100°C for 2 hours.

[0055] After filtration and washing of the residue with ethanol (250 cm^3) evaporation of the filtrate gave the crude material. Recrystallisation from butan-1-ol (10 cm^3) gave BRL 42810, 5.1g (70%), m.p. 102°C. This material was consistent with that prepared previously.

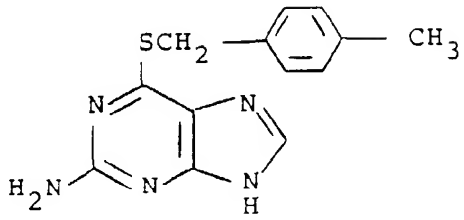
[0056] ^{1}H n.m.r. ($CDCl_3$): δ 1.90(m, 3H,-CH_2CH-), 2.00(s,6H,-CH_3), 4.05 (d,4H,OCH_2-), 4.10(t,2H,NCH_2-), 5.35(brs, 2H,NH_2), 7.70(s,1H,H-8), 8.60(s,1H,H-6).

[1] Prepared by the method of G.H. Hitchings et. al., US 3232938.

Example 3

a) 2-Amino-6-[(4-methylphenyl)methylthio]purine

[0057]

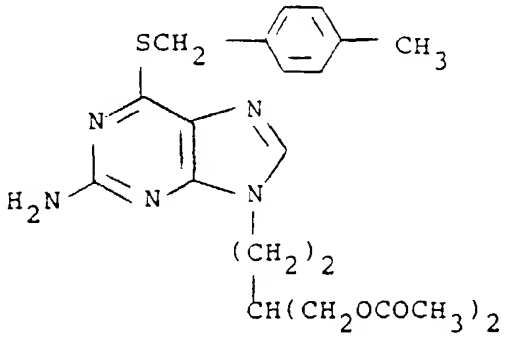


[0058] A mixture of thioguanine (25g), α-chloro-p-xylene (21g) and potassium carbonate (30g) in N,N-dimethylformamide (500cm^3) was stirred at ambient temperature overnight. The reaction mixture was filtered and the filtrate evaporated to give a yellow solid. Recrystallisation from methanol (100cm^3) gave 25.7g (64%) of the title compound, m.p. 240-242°C

[0059] ^{1}H n.m.r. (D^{6}DMSO): δ 2.25 (s, 3H, -C$\underline{H}_3$), 4.50 (s, 2$\underline{H}$, SC$\underline{H}_2$-), 6.45 (brs, 2H, -N$\underline{H}_2$), 7.10 (d, 2H, C$_6\underline{H}_4$-), 7.35 (d, 2H, C$_6\underline{H}_4$), 7.90 (s, 1H, $\underline{H}$-8), 12.55 (brs, 1H, >NH).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine

[0060]

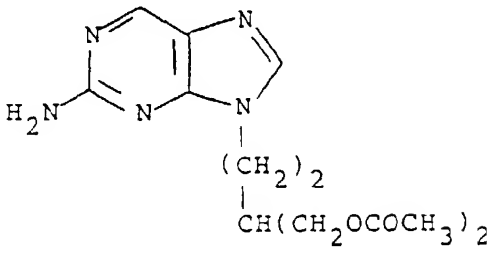


[0061] Using the previously described procedure 2-amino-6-[(4-methylphenyl)methylthio]purine (25g) and 2-acetoxymethyl-4-iodobut-1-yl acetate (29g) gave the title compound 33.3g (79%) m.p. 102-103°C, and 4.2g (9.9%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine

[0062] ^{1}H n.m.r. (D^{6}DMSO) of the title compound: δ 1.85 (m, 3H, -C$\underline{H}_2$C$\underline{H}$<), 2.00 (s, 6H, C$\underline{H}_3$CO-), 2.25 (s, 3H, -C$\underline{H}_3$), 4.00 (d, 4H, -OC$\underline{H}_2$-), 4.10 (t, 2H, -NC$\underline{H}_2$), 4.50 (s, 2H, -SC$\underline{H}_2$), 6.60 (brs, 2H, -N$\underline{H}_2$), 7.10 (d, 2H, C$_6\underline{H}_4$) 7.30 (d, 2H, C$_6\underline{H}_4$), 7.95 (s, 1H, $\underline{H}$-8).

c) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-purine, (BRL42810

[0063]



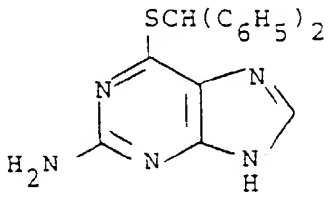
[0064] Raney nickel (3g) was added to a solution of 9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine (10g) in ethanol (250cm^3) and the mixture treated with hydrogen at 100° and 100 psi for 40 hours. Filtration and evaporation of the filtrate gave the crude compound. Recrystallisation from butan-1-ol (18 cm^3) gave the title compound 4.2g (60%). m.p. 100-102°C

[0065] ^{1}H n.m.r. ($CDCl_3$) and t.l.c (60:40 ethylacetate: methanol) were consistent with the title compound.

Example 4

a) 2-Amino-6-[(diphenylmethyl)thio]purine

[0066]

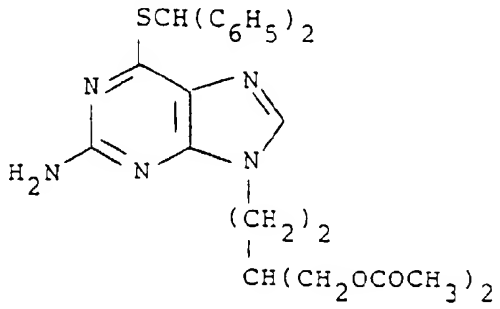


[0067] A mixture of thioguanine (25g), bromodiphenylmethane (37.1g) and potassium carbonate (31.1g) in N,N-dimethylformamide (250cm^3) was stirred at ambient temperature for 66 hours. The reaction mixture was filtered and the filtrate evaporated to give a cream solid. Recrystallisation from methanol gave 24g (48%) of the title compound, m.p. 226-227°C

[0068] ^{1}H n.m.r. (D_6DMSO): δ 6.35 (s, 2H, -N$\underline{H}_2$), 6.70 (s, 1H, SC$\underline{H}$<), 7.30 (m, 6H, $C_6\underline{H}_5$-), 7.50 (d, 4H, $C_6\underline{H}_5$-), 7.90 (s, 1H, $\underline{H}$-8), 12.50 (brs, 1H, >N-$\underline{H}$).

b) 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine

[0069]



[0070] A mixture of 2-amino-6-[(diphenylmethyl)thio]purine (6.7g), 2-acetoxymethyl-4-iodobut-1-yl acetate (7.0g) and anhydrous potassium carbonate (4.14g) in N,N-dimethylformamide (100cm^3) was stirred at ambient temperature overnight. The reaction mixture was filtered and the residue washed with N,N-dimethylformamide (100cm^3). Evaporation of the filtrate gave a pale coloured oil. Purification via column chromatography on silica (450g) [eluant 3% methanol-dichloromethane] gave the title compound 9.3g (89%) as a viscous gum and 1.1g (10.5%) of 7-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine.

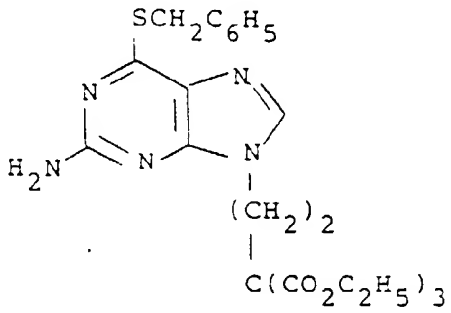
[0071] ^{1}H n.m.r. ($CDCl_3$) of the title compound δ 1.85 (m, 3H, -C$\underline{H}_2$C$\underline{H}$<), 2.05 (s, 6H, C$\underline{H}_3$) 4.15 (d, 6H, -NC$\underline{H}_2$ + -OC$\underline{H}_2$-), 5.2 (s, 2H, -N$\underline{H}_2$) 6.2 (s, 1H, -SC$\underline{H}$<) 7.25 (m, 6H, C$_6\underline{H}_5$-), 7.5 (d, 4H, C$_6\underline{H}_5$), 7.65 (s, 1H, $\underline{H}$-8)

[0072] Mass spectrum of the title compound : m/e 519 (m$^+$), main fragment ions at 277, 255, 199, 167 and 91.

Example 5

a) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine

[0073]

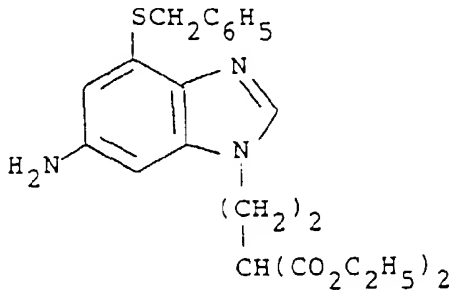


[0074] Ethyl 4-bromo-2,2-dicarboethoxybutanoate (14.5g) was added to a stirred suspension of 2-amino-6-[(phenylmethyl)thio]purine (11.4g) and anhydrous potassium carbonate (9.15g) in N,N-dimethylformamide (100cm^3) and the resulting mixture stirred at 40° overnight. When cool the mixture was filtered and the filtrate evaporated to give a pale coloured viscous gum. Purification via silica gel chromatography (eluant dichloromethane increasing to 10% methanol-dichloromethane) gave 11.42g (50%) of the title compound, m.p. 100-102°. A second compound, 5.38g, was identified as 2-amino-9-(ethyl 2-carboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine, m.p. 86-88°. A mixed fraction containing 2.15g of the corresponding N7-substituted di- and tri- carboethoxybutanoates was also isolated.

[0075] ^{1}H n.m.r. ($CDCl_3$) of the title compound: δ 1.25(t, 9H, -C$\underline{H}_3$), 2.65(t, 2H, -C$\underline{H}_3$C -), 4.25 (m, 8H, -NC$\underline{H}_2$- + -C$\underline{H}_2$CH$_3$), 4.55 (s, 2H, - SC$\underline{H}_2$ -) 5.10(brs, 2H, -N$\underline{H}_2$). 7.25(m, 3H, C$_6\underline{H}_5$-), 7.40 (d,2H, C$_6\underline{H}_5$-), 7.609(s, 1H, $\underline{H}$-8).

b) 2-Amino-9-(ethyl 2 -carboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine

[0076]



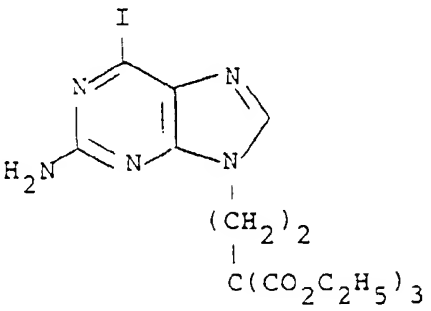
[0077] 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine (3g) was added to a solution of sodium (0.4g) in ethanol (20cm^3) and the mixture stirred at ambient temperature for 15 minutes. T.l.c. (2% methanol-dichloromethane), one-spot rf 0.40. The solution was neutralised with 2M-hydrochloric acid and water (100cm^3) added. The mixture was extracted with dichloromethane (2 x 50 cm^3) and the extract dried over magnesium sulphate. Filtration and evaporation of the filtrate gave the crude material. Purification via column chromatography on silica (40g) [eluant dichloromethane increasing to 5% methanol-dichloromethane] gave the title compound 1.2g (46.5%) as a viscous gum which slowly crystallised on standing at ambient temperature, m.p. 86-88°C.

[0078] ^{1}H n.m.r. ($CDCl_3$): δ 1.25 (t, 6H, C$\underline{H}_3$), 2.30 (m, 2H, CHC$\underline{H}_2$-), 3.20(t, 1H, CC$\underline{H}$C), 4.00 (m, 6H, -NC$\underline{H}_2$ + -C$\underline{H}_2$CH$_3$), 4.40(s, 2H, SC$\underline{H}_2$-), 5.50 (brs, 2H, -N$\underline{H}_2$), 7.10(q, 3H, C$_6\underline{H}_5$), 7.25 (d, 2H, C$_6\underline{H}_5$-), 2.50 (s, 1H, $\underline{H}$-8).

Example 6

a) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine

[0079]



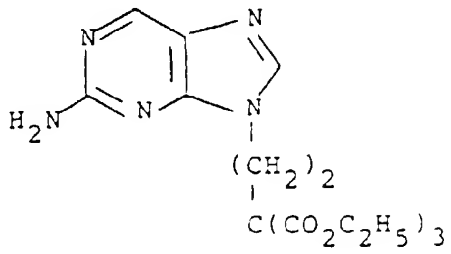
[0080] A mixture of 2-amino-6-iodopurine (10g), ethyl 4-bromo-2,2-dicarboethoxybutanoate (13g) and anhydrous potassium carbonate (8.0g) in N,N-dimethylformamide (150 cm^3) was stirred at 40°C overnight. The mixture was filtered and the filtrate evaporated to leave a pale yellow solid. The solid was dissolved in 2% methanol-dichloromethane and column chromatographed on silica (200g) [eluant = 2% methanol-dichloromethane] to give the title compound 13.8g (69.4%) and 1.5g (7.5%) of 2-amino-7-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine.

[0081] m.p. (of title compound) 99-102°C

[0082] ^{1}H n.m.r. (D^6 -DMSO) of title compound: δ 1.20(t, 9H, -CH$_2$C$\underline{H}_3$), 2.60 (t, 2H, -C$\underline{H}_2$C-), 4.15(q, 6H, -C$\underline{H}_2$CH$_3$), 4.50(t, 2H, N-C$\underline{H}_2$), 6.80(brs, 2H, -N$\underline{H}_2$), 8.00(s, 1H, $\underline{H}$-8).

b) 2-Amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)purine

[0083]



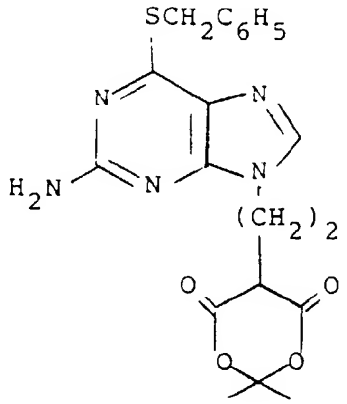
[0084] A mixture of 2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine (85g), triethylamine (25.25 cm^3) and 5% palladium on charcoal (10g) in ethanol (1,500 cm^3) was hydrogenated at 100 psi and 50°C for 2 hours. T.l.c. (10% methanol-chloroform) showed one spot, rf = 0.40. When cool the mixture was filtered and the filtrate evaporated to leave a solid. The solid was dissolved in water (1000 cm^3) and extracted with chloroform (3 x 500 cm^3). The organic extracts were combined, dried over magnesium sulphate and evaporated to give the title compound 62.2g (96%) as an oil which crystallised on standing.

[0085] ^1H n.m.r. (D^6 -DMSO): 1.20(t,9H, $-CH_2\underline{CH_3}$), 2.65(t,2H, $-\underline{CH_2}C-$), 4.15(q,6H, $-\underline{CH_2}CH_3$), 4.35(t,2H, $N-\underline{CH_2}$), 6.50(brs, 2H, $-N\underline{H_2}$), 7.95(s, 1H,H-8), 8.65(s, 1H, H-6).

Example 7

2-Amino-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl) eth-2-yl]-6-[(phenylmethyl)thio]purine

[0086]



[0087] A mixture of 2-amino-6-[(phenylmethyl)thio]purine (1.0g), 2,2-dimethyl-1,3-dioxaspiro[2.5]octane-4,6-dione (0.7g) and potassium carbonate (1.0g) in dry N,N-dimethylformamide (10 cm^3) was stirred at ambient temperature for 18 hours. The mixture was filtered and the filtrate evaporated. T.l.c. (20% methanol-dichloromethane) showed two products, rf = 0.3 and 0.1, corresponding to the potassium salts of the title compound and the N-7 isomer respectively. Proton n.m.r. evidence suggested a product ratio of 2.7:1.

[0088] The residue was dissolved in water, acidified to pH 4 with dilute hydrochloric acid and extracted with dichloromethane (2 x 100 cm^3). The organic layers were combined, dried (magnesium sulphate) and evaporated to give a yellow solid.

[0089] Purification by column chromatography on silica [eluant = 5% methanol-dichloromethane] gave the title compound that was recrystallised from boiling ethyl acetate (0.2g, 12%).

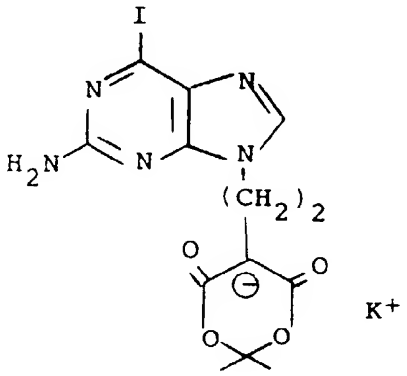
[0090] ^{1}H n.m.r. (D^6-DMSO): δ 1.68(s, 3H, -C$\underline{H}_3$), 1.83(s, 3H, -C$\underline{H}_3$), 2.39(m, 2H, $\underline{H}$-2'), 4.26(m, 2H, $\underline{H}$-1'), 4.50(m, 1H,$\underline{H}$-3'), 4.56(s, 2H, -$\underline{CH}_2C_6H_5$), 6.54(brs, 2H, -$\underline{NH}_2$), 7.19-7.49 (m, 5H, -CO$\underline{H}_5$), 7.95(s, 1H, $\underline{H}$-8).

$C_{20}H_{21}N_5O_4S$	requires	C,56.19; H,4.95; N,16.38%
	found	C,55.97; H,4.94; N,16.04%

Example 8

2-Amino-6-iodo-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt

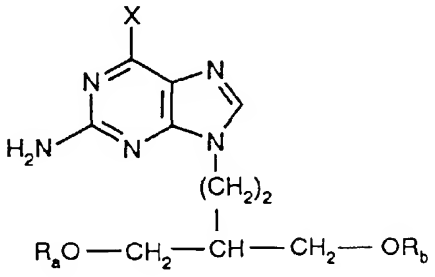
[0091]



[0092] A mixture of 2-amino-6-iodopurine (1.3g), 2,2-dimethyl-1,3-dioxaspiro[2.5]octane-4,6-dione (0.85g) and potassium carbonate (1.2g) in N,N-dimethylformamide (20 cm^3) was stirred at ambient temperature for 18 hours. The mixture was filtered and the solvent evaporated. Proton n.m.r. spectroscopy suggested a mixture of the title compound and 2-amino-6-iodo-7-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt in the ratio of 2.8:1. ^{1}H n.m.r. (D^6-DMSO): of the title compound: δ 1.40(s, 6H, -C$\underline{H}_3$), 2.64(t, 2H, $\underline{H}$-2'), 4.04(t, 2H, $\underline{H}$-1'), 6.75(brs, 2H, -N$\underline{H}_2$), 7.96(s, 1H, $\underline{H}$-8).

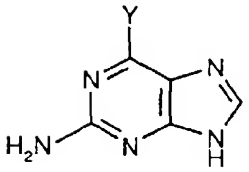
Claims

1. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



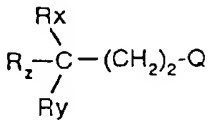
(I)

wherein X is hydrogen or hydroxy and R_a and R_b are independently hydrogen or a group RCO- wherein R is phenyl or C_{1-18} alkyl;
which process comprises reacting a compound of formula (II):



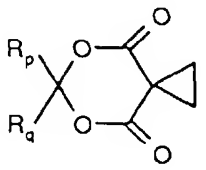
(II)

wherein the amino group is optionally protected, Y is iodo, diphenylmethylthio or benzylthio wherein the phenyl moiety is optionally substituted by one or two groups selected from C_{1-4} alkyl, halo and C_{1-4} alkoxy, with a compound of formula (III):



(III)

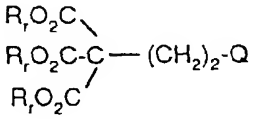
wherein Q is a leaving group; R_x and R_y are protected hydroxymethyl or acyloxymethyl, or group(s) convertible to hydroxymethyl or acyloxymethyl; and R_z is hydrogen or a group convertible thereto; or a compound of formula (IIIA):-



(IIIA)

wherein R_p and R_q are independently hydrogen, C_{1-6} alkyl or phenyl, or R_p and R_q together are C_{4-6} polymethylene; and thereafter converting Y to X is hydroxy by means of hydrolysis, or to X is hydrogen by means of reduction; converting R_x and R_y, when other than hydroxymethyl or acyloxymethyl, to hydroxymethyl or acyloxymethyl; optionally converting R_x/R_y hydroxymethyl to acyloxymethyl or vice versa; deprotecting the 2-amino group where necessary; converting R_z, when other than hydrogen, to hydrogen; and optionally forming a pharmaceutically acceptable salt thereof.

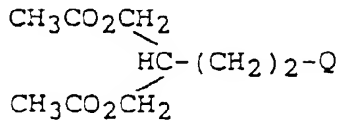
2. A process according to claim 1 wherein the compound of formula (III) is of formula (IIIB):



(IIIB)

wherein R_r is C_{1-6} alkyl or phenyl C_{1-6} alkyl, in which any phenyl moieties are optionally substituted by one or two groups selected from C_{1-4} alkyl, halo and C_{1-4} alkoxy.

3. A process according to claim 1 wherein the compound of formula (III) is of formula (III)':



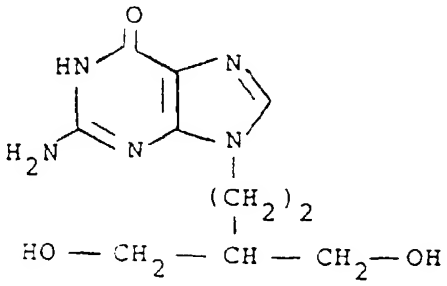
(III)'

wherein Q is a leaving group.

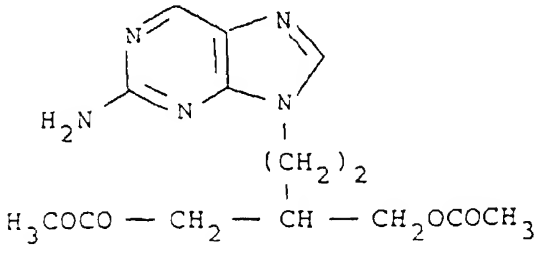
4. A process according to claim 1, 2 or 3 wherein Y is iodo.

5. A process according to any one of claims 1 to 4 wherein Q is halo, tosyloxy or mesyloxy.

6. A process according to any one of claims 1 to 5 for the preparation of a compound of formula (A) or (B):

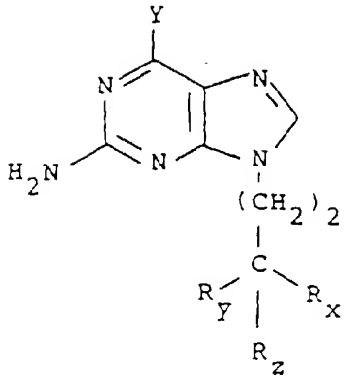


(A)



(B)

7. An intermediate of formula (IV):



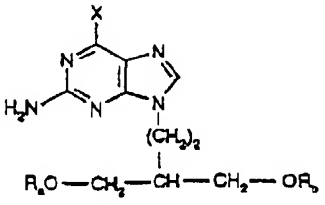
(IV)

wherein Y, R_x, R_y and R_z are as defined in claim 1.

8. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodopurine,
9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purine,
9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purine,
9-(4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purine,
2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-[(phenylmethyl)thio]purine,
2-amino-9-(ethyl 2,2-dicarboethoxybutanoate-4-yl)-6-iodopurine,
2-amino-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]-6-[(phenylmethyl)thio]purine,
2-amino-6-iodo-9-[1-(2,2-dimethyl-1,3-dioxane-4,6-dione-5-yl)eth-2-yl]purine potassium salt, or
9-((4-acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenacylmethyl)thio]purine.

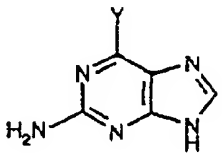
Patentansprüche

1. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon:



(I)

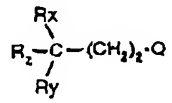
worin X ein Wasserstoffatom oder eine Hydroxylgruppe bedeutet und R_a und R_b unabhängig Wasserstoffatome oder Reste RCO- bedeuten, worin R eine Phenylgruppe oder einen C_{1-18}-Alkylrest bedeutet;
wobei das Verfahren umfaßt: Umsetzung einer Verbindung der Formel (II):



(II)

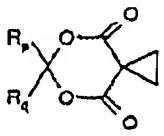
worin die Aminogruppe gegebenenfalls geschützt ist, Y ein Iodatom, eine Diphenylmethylthio- oder Benzylthio-

gruppe bedeutet, worin die Phenyleinheit gegebenenfalls mit einem oder zwei aus C_{1-4}-Alkylresten, Halogenatomen und C_{1-4}-Alkoxyresten ausgewählten Resten substituiert ist, mit einer Verbindung der Formel (III):



(III)

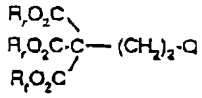
worin Q eine Abgangsgruppe bedeutet; R_x und R_y geschützte Hydroxymethyl- oder Acyloxymethylgruppen oder (einen) in eine Hydroxymethyl- oder Acyloxymethylgruppe überführbare(n) Rest(e) bedeuten; und R_z ein Wasserstoffatom oder einen hierzu überführbaren Rest bedeutet; oder einer Verbindung der Formel (IIIA):



(IIIA)

worin R_p und R_q unabhängig Wasserstoffatome, C_{1-6}-Alkylreste oder Phenylgruppen bedeuten oder R_p und R_q zusammen einen C_{4-6}-Polymethylenrest bedeuten; und anschließend Überführen von Y in X = eine Hydroxylgruppe mittels Hydrolyse oder in X = ein Wasserstoffatom mittels Reduktion; Überführen von R_x und R_y, wenn sie von Hydroxymethyl- oder Acyloxymethylgruppen verschieden sind, in Hydroxymethyl- oder Acyloxymethylgruppen; gegebenenfalls Überführen von R_x/R_y = Hydroxymethylgruppen in Acyloxymethylgruppen oder umgekehrt; Entfernung der Schutzgruppe von der 2-Aminogruppe, falls nötig; Überführen von R_z, wenn es von Wasserstoff verschieden ist, in ein Wasserstoffatom; und gegebenenfalls Herstellung eines pharmazeutisch verträglichen Salzes davon.

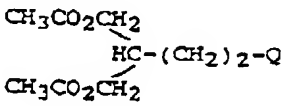
2. Verfahren nach Anspruch 1, wobei die Verbindung der Formel (III) die Formel (IIIB) aufweist:



(IIIB)

worin R_r einen C_{1-6}-Alkyl- oder Phenyl-C_{1-6}-alkylrest bedeutet, worin jede der Phenyleinheiten gegebenenfalls mit einem oder zwei aus C_{1-4}-Alkylresten, Halogenatomen und C_{1-4}-Alkoxyresten ausgewählten Resten substituiert ist.

3. Verfahren nach Anspruch 1, wobei die Verbindung der Formel (III) die Formel (III)' aufweist:



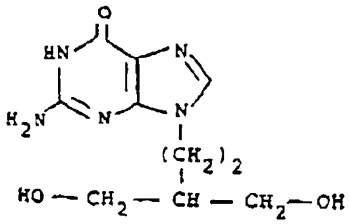
(III)'

worin Q eine Abgangsgruppe bedeutet.

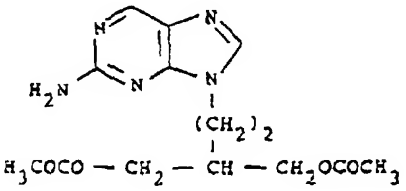
4. Verfahren nach Anspruch 1, 2 oder 3, wobei Y ein Iodatom bedeutet.

5. Verfahren nach einem der Ansprüche 1 bis 4, wobei Q ein Halogenatom, eine Tosyloxy- oder Mesyloxygruppe bedeutet.

6. Verfahren nach einem der Ansprüche 1 bis 5 zur Herstellung einer Verbindung der Formel (A) oder (B):

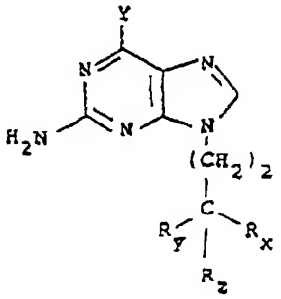


(A)



(B)

7. Intermediärverbindung der Formel (IV):



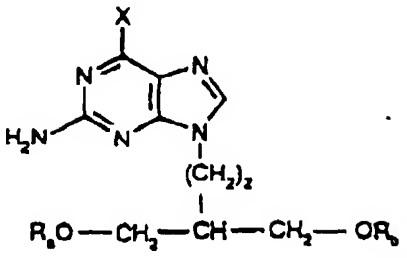
(IV)

worin Y, R_x, R_y und R_z wie in Anspruch 1 definiert sind.

8. 9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-iodpurin,
9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenylmethyl)thio]purin,
9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(4-methylphenyl)methylthio]purin,
9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(diphenylmethyl)thio]purin,
2-Amino-9-(ethyl-2,2-dicarboethoxybutanoat-4-yl)-6-[(phenylmethyl)thio]purin,
2-Amino-9-(ethyl-2,2-dicarboethoxybutanoat-4-yl)-6-iodpurin,
2-Amino-9-[1-(2,2-dimethyl-1,3-dioxan-4,6-dion-5-yl)eth-2-yl]-6-[(phenylmethyl)thio]purin,
2-Amino-6-iod-9-[1-(2,2-dimethyl-1,3-dioxan-4,6-dion-5-yl)eth-2-yl]purin-Kaliumsalz, oder
9-(4-Acetoxy-3-acetoxymethylbut-1-yl)-2-amino-6-[(phenacylmethyl)thio]purin.

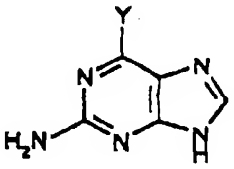
Revendications

1. Procédé de préparation d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci :



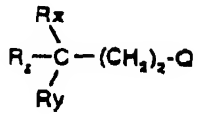
(I)

où X est un hydrogène ou un hydroxy et R_a et R_b sont indépendamment un hydrogène ou un groupe RCO-, dans lequel R est un phényle ou un alkyle en C_{1-18} ;
lequel procédé comprend la réaction d'un composé de formule (II) :



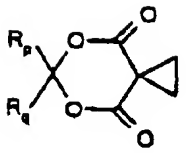
(II)

dans laquelle le groupe amino est éventuellement protégé, Y est un iodo, un diphénylméthylthio ou un benzylthio dans lequel le groupement phényle est éventuellement substitué par un ou deux groupes choisis parmi un alkyle en C_{1-4}, un halogéno et un alcoxy en C_{1-4}, avec un composé de formule (III) :



(III)

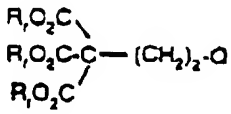
dans laquelle Q est un groupe partant ; R_x et R_y sont un hydroxyméthyle ou acyloxyméthyle protégé, ou un (des) groupe(s) pouvant être transformé(s) en un hydroxyméthyle ou acyloxyméthyle ; et R_z est un hydrogène ou un groupe pouvant être transformé en celui-ci ; ou un composé de formule (IIIA) :



(IIIA)

dans laquelle R_p et R_q sont indépendamment un hydrogène, un alkyle en C_{1-6} ou un phényle, ou R_p et R_q sont conjointement un polyméthylène en C_{4-6} ; et ensuite la transformation de Y en X = hydroxy par hydrolyse, ou en X = hydrogène par réduction ; la transformation de R_x et R_y, lorsqu'ils sont différents d'un hydroxyméthyle ou d'un acyloxyméthyle, en un hydroxyméthyle ou un acyloxyméthyle ; éventuellement la transformation de R_x/R_y hydroxyméthyle en acyloxyméthyle ou vice versa ; la déprotection du groupe 2-amino lorsque cela est nécessaire ; la transformation de R_z, lorsqu'il est différent d'un hydrogène, en hydrogène ; et éventuellement la formation d'un sel pharmaceutiquement acceptable de celui-ci.

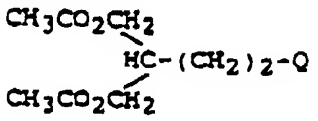
2. Procédé selon la revendication 1, dans lequel le composé de formule (III) et de formule (IIIB) :



(IIIB)

dans laquelle R_r est un alkyle en C_{1-6} ou un phényl-C_{1-6}-alkyle, dans lequel tous groupements phényle sont éventuellement substitués par un ou deux groupes choisis parmi un alkyle en C_{1-4}, un halogéno et un alcoxy en C_{1-4}.

3. Procédé selon la revendication 1, dans lequel le composé de formule (III) est de formule (III)' :



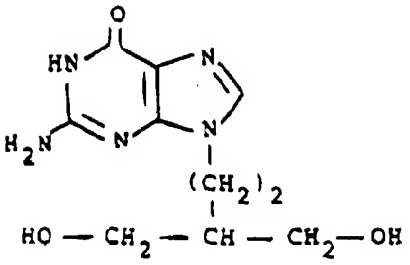
(III)'

dans laquelle Q est un groupe partant.

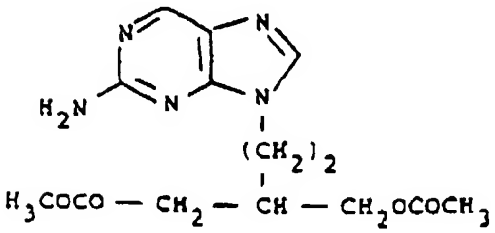
4. Procédé selon la revendication 1, 2 ou 3, dans lequel Y est un iodo.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel Q est un halogéno, un tosyloxy ou un mésyloxy.

6. Procédé selon l'une quelconque des revendications 1 à 5, destiné à la préparation d'un composé de formule (A) ou (B) :

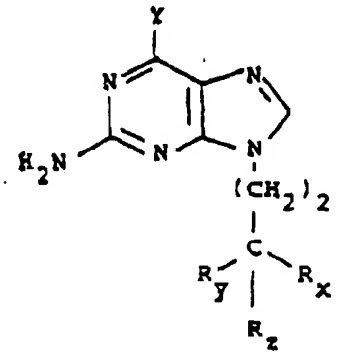


(A)



(B)

7. Intermédiaire de formule (IV) :



(IV)

dans laquelle Y, R_x, R_y et R_z sont tels que définis à la revendication 1.

8. 9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-iodopurine,
9- (4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(phénylméthyl)thio]purine,
9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(4-méthylphényl)méthylthio]purine,
9-(4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[(diphénylméthyl)thio]purine,
2-amino-9-(éthyl 2,2-dicarboéthoxybutanoate-4-yl)-6-[(phénylméthyl)thio]purine,
2-amino-9-(éthyl 2,2-dicarboéthoxybutanoate-4-yl)-6-iodopurine,
2-amino-9-[1-(2,2-diméthyl-1,3-dioxane-4,6-dione-5-yl)éth-2-yl]-6-[(phénylméthyl)thio]purine,
sel de potassium de 2-amino-6-iodo-9-[1-(2,2-diméthyl-1,3-dioxane-4,6-dione-5-yl)éth-2-yl]-purine, ou
9-((4-acétoxy-3-acétoxyméthylbut-1-yl)-2-amino-6-[phénacylméthyl)thio]purine.